CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS, WASHINGTON, D.C. 20231, ON 20 JUNE 1997

Mary E. McCarthy
AGENT/ATTORNEY FOR APPLICANT

20 June 1997
DATE

Attorney Docket No. P50317

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Lukas-Laskey, et al.	June 20, 1997
Serial No.:	08/483,635	Group Art Unit No.: 1205
Filed:	June 7, 1995	Examiner: W. Jarvis
For:	METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE	

DECLARATION OF MARTIN WEHLING

I, MARTIN WEHLING, M.D., a citizen of Germany, do hereby declare:

1. THAT I am a full professor for clinical pharmacology and director of the institute of clinical pharmacology, faculty of clinical medicine Mannheim, University of Heidelberg and that I have held this post since 1995;

2. THAT I head the division of clinical pharmacology and head the Klinische Forschergruppe (clinical research group) "clinical pharmacology", the Deutsche Forschungsgemeinschaft, and that I have held this appointment since 1994;

3. THAT I began my study of chemistry and medicine at the University of Kiel in 1975, that I received my full approbation as a physician in 1981, and that I became qualified as an internist in 1990, as a cardiologist in 1992 and as a clinical pharmacologist in 1993;

4. THAT by reason of my qualifications and experience I consider myself an expert in the field of medicine, cardiology and clinical pharmacology;

5. THAT I have read and understood the above-identified patent application and have read and understood the Office Action dated December 20, 1996;

6. THAT it has been shown in well-controlled clinical trials that neither α_1-adrenoceptor antagonists [Cohn et al., *N Engl J Med*, 314: 1547-1552 (1986)] nor a β-blocker, metoprolol, [Waagstein et al., *Lancet*, 342: 1441-1446 (1993)] decrease mortality in CHF patients; significantly

7. THAT, in my opinion based on the clinical data of known α_1-adrenoceptor antagonists and β-blockers, reduction of mortality with α-adrenoceptor antagonists or with β-blockers was an unmet need in the treatment of CHF, which could not be expected to be achieved by a combined α_1/β-blocker, such as carvedilol;

8. THAT, in my opinion based on the clinical data of known α_1-adrenoceptor antagonists and β-blockers, it would not be obvious, even to one skilled in the art, to administer an α_1/β-adrenoceptor antagonist, such as carvedilol, to decrease mortality in CHF patients;

9. THAT β-blockers have been contraindicated in patients suffering from CHF because they are known to have undesireable cardiodepressive effects;

10. THAT, in my opinion based on the data of known β-blockers, the reduction in all-cause mortality in CHF patients treated with carvedilol disclosed in the above-referenced application is unexpected and significant;

11. THAT the doses and the dosing schedules in CHF patients are quite different from those used in other indications, such as hypertension, in that the initial doses are much lower, but the target doses - after up-titration - are higher than those commonly used in hypertension;

12. THAT, in my opinion, the doses and the dosing schedules of carvedilol cannot be regarded as obvious since side-effects are avoided and reduction in mortality is achieved using doses different from those used in other indications;

13. THAT monitoring the mortality rate in the clinical trials described in the above-referenced application was not a pre-specified endpoint and that evaluating the effect of carvedilol on the survival of patients with CHF was prospectively designed into said clinical trials;

14. THAT, in my opinion, the discovery that carvedilol reduced mortality by about 67% in CHF patients satisfies a long-felt need which was recognized, but not solved, by others, as evidenced by the fact that standard agents for treating CHF, such as diuretics, digitalis glycosides, vasodilators (excluding ACE inhibitors), and ionotropic agents, relieve the symptoms of the disease, but are not known to reduce the mortality rate in CHF patients, and that even though ACE inhibitors reduce mortality in CHF patients, this reduction is only on the order of about 20%;

15. THAT certain agents, such as milrinone [Di Bianco, et al., *N Engl J Med*, 320: 677-683 (1989)], flosequinan [Anonymous, *Clin Pharmacy*, 12, 474 and 713 (1993)] and vesnarinone [Feldman, et al., *J Am Coll Cardiol*, 29, 7105 (1997)], relieve the symptoms of CHF, but increase the mortality of CHF patients;

16. THAT an independent drug safety monitoring board was installed to oversee the clinical trials described in the above-referenced application so as to stop the trials prematurely if increased mortality rates were observed in the cavedilol-treated CHF patients;

17. THAT the independent drug safety monitoring board recommended stopping the clinical trials on the basis that the placebo-treated patients, not the carvedilol-treated patients, had an excess mortality when the two groups were compared;

18. THAT, in my opinion, one of ordinary skill in the art would conclude that carvedilol exhibits a surprisingly and unexpectedly superior property when compared to other agents for treating CHF, and thus that carvedilol provides superior treatment for congestive heart failure, when compared to known agents, since it reduces mortality in CHF patients by about 67%.

Serial No.: 08/483,635
Group Art Unit No.: 1205

19. THAT I further declare that all the statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the present application or of any patent issuing thereon.

M. Wehling

Martin Wehling, M.D.

6/19/97

Date

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Court No. T-84-02

FEDERAL COURT – TRIAL DIVISION

BETWEEN:

HOFFMANN-LA ROCHE LIMITED,
- and -
SMITHKLINE BEECHAM CORPORATION,

Applicants,

AND:

THE MINISTER OF HEALTH,
- and -
NOVOPHARM LIMITED,

Respondents.

AFFIDAVIT OF DR. MARY ANN LUKAS

I, **MARY ANN LUKAS**, physician, of the City of Pasadena, in the State of Maryland, **MAKE OATH AND SAY:**

I. ACADEMIC AND PROFESSIONAL QUALIFICATIONS

1. I am currently Director, Cardiovascular Therapeutic Area, North American Medical Affairs for the Applicant, GlaxoSmithKline Inc. [Hereinafter, "GSK"].

2. I received my Bachelor of Science from Kings College in 1976 and received my M.D. from the University of Pennsylvania, Philadelphia, Pennsylvania in 1980. My Internal Medicine internship and residency (1984), and my fellowship in Cardiology (1988) were also done at the University of Pennsylvania. I am a diplomate of the American Board of Internal Medicine (1984) and also hold a subspecialty certification in Cardiology (1988).

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3. Following the completion of my fellowship in Cardiology at the University of Pennsylvania, and after holding a practice and teaching position at Hahnemann University, I joined the Cardiovascular Therapeutic Unit of what was then SmithKline & French in 1988. Since that time I have remained in various capacities within what is now GSK in the Cardiopulmonary Therapeutic Unit and have had direct involvement and leadership roles in the development of carvedilol throughout that time.

4. I am currently a Fellow of the American College of Cardiology and the American College of Physicians and an active member of the Heart Failure Society of America. I am also a member of Alpha Omega Alpha (US national medical honor society).

5. Attached as **Exhibit "A"** to this affidavit is a copy of my *curriculum vitae* setting out in further detail my qualifications and professional expertise.

6. Based on my experience and activities as a physician and clinical research scientist as set out in my *curriculum vitae* at **Exhibit "A"**, and as co-inventor of Canadian Patent No. 2,212,548 (the "'548 Patent"), I do verily believe that I can comment on the knowledge possessed by a person skilled in the treatment of cardiovascular disease from the late 1980's to present.

II. CANADIAN LETTERS PATENT NO. 2,212,548

7. I am one of the named inventors of the '548 Patent entitled "Use of Carbazole Compounds for the Treatment of Congestive Heart Failure". The '548 Patent was filed in Canada on February 7, 1996 and issued on August 24, 1999. Attached hereto as **Exhibit "B"** to my affidavit is a copy of the '548 Patent.

8. The '548 Patent claims priority from German Patent Application No. 19503995.5 dated February 8, 1995 (the "German Application") and U.S. Patent Application No. 08/483,635 dated June 7, 1995 (the "U.S. Application"). Attached as **Exhibit "C"** to my affidavit is a copy of the German Application. Attached as **Exhibit "D"** to my affidavit is a copy of the English translation of the German Application. Attached as **Exhibit "E"** to my affidavit is a copy of the U.S. Application.

III. MANDATE

9. I have reviewed the Notice of Allegation forwarded by Novopharm Limited ("Novopharm") to Hoffmann-La Roche Limited dated November 28, 2001 (the "Notice of Allegation" or "NOA"), attached hereto as **Exhibit "F"**. I have also reviewed the publications identified on pages 5 and 6, items (a) to (n) of the NOA, as well as the publications identified at Appendices A and B thereto. These publications are referred to and discussed below.

10. I have been asked to comment on the history of the development of carvedilol by GSK from its use in the treatment of hypertension, to its use in the symptomatic treatment of Congestive Heart Failure ("CHF") and finally for use in the reduction of mortality resulting from CHF. In addition, I have also been asked to comment on the allegations of invalidity contained in the NOA with respect to the '548 Patent as outlined below.

Anticipation

11. In the Notice of Allegation, Novopharm alleges that the subject matter covered by the claims of the '548 Patent are invalid given that they are anticipated as follows:

> Anticipation
>
> The claims in the '548 Patent are overly broad, claiming more than that in respect of which the patentee, or the person through whom the patentee claims, was the first inventor. The patentee or inventor was not the first to invent.
>
> The subject matter covered by claims 1-52 was known prior to the claim date (here the priority filing date of the application). Representative prior art that discloses this subject matter and made the subject matter of the invention available to the public in Canada or elsewhere is listed in Appendices "A" and "B". In particular, the following was known:
>
> (a) the use of carvedilol in the treatment of CHF. Without limitation, the claims 12-14, 29-37, 40, 41, 47-52 do not refer to decreasing mortality resulting from CHF.;
>
> (b) the use of carvedilol in decreasing mortality resulting from CHF;
>
> (c) the use of carvedilol with at least one therapeutic agent selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics and cardiac glycosides;
>
> (d) the use of carvedilol at dosages of 12.5 mg and 25 mg;

(e) the use of 3.125 mg carvedilol twice daily for 7 days, 6.25 mg and then 12.5 mg for the next 7 days and 25 mg twice daily for the following 7 days;

(f) a standard titration dose of carvedilol starting at 3.125 and building to a final dose of between 25 and 75 mg a day was known; and

(g) the use of carvedilol in the form of a pharmaceutical formulation comprising carvedilol or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for the treatment of CHF.

12. I am advised by counsel for Ogilvy Renault that Novopharm will apparently rely upon the following references from Appendices A and B to Novopharm's NOA, as set out in a letter of Heenan Blaikie dated February 18, 2002. I further understand from Ogilvy Renault and the letter of Heenan Blaikie of February 18, 2002 that Novopharm alleges "that each of the listed pieces of prior art *on its own* anticipated the ['548] patent":

i) Senior, R. et al., *Effects of Carvedilol on Ventricular Arrhythmias*; J. Cardiovasc. Pharmacol., Vol. 19 (Suppl. 1), 1992; (Appendix "A" – 1992.7)

ii) Kelly, D.T.; *Carvedilol in Heart Failure*; Cardiology 1993; 82 (suppl. 3):45-49; (Appendix "A" – 1993.7)

iii) Ohlstein, E., United States Patent No. 5,308,862 issued May 3, 1994 based on Application No. 26,892 filed March 5, 1993 for an invention entitled USE AND METHOD OF TREATMENT USING CARBAZOLYL-(4)-OXYPROPANOLAMINE COMPOUNDS FOR INHIBITION OF SMOOTH MUSCLE CELL PROLIFERATION; (Appendix "A" – 1994.9)

iv) Appelgren *et al.*, United States Patent No. 4,888,179 issued December 19, 1989 based on Application No. 144,229 filed January 15, 1988 for an invention entitled DIURETIC COMPOSITION; (Appendix "A" – 1989.2)

v) Finkelstein et al., United States Patent No. 5,312,823 issued May 17, 1994 based on Application No. 746,024 filed August 14, 1991 for an invention entitled SUBSTITUTED IMIDAZOLES HAVING ANGIOTENSIN II RECEPTOR BLOCKING ACTIVITY; (Appendix "A" – 1994.4)

vi) Das Gupta, P. *et al.*, *The Effects of Intravenous Carvedilol, a New Multiple Action Vasodilatory Beta-Blocker, in Congestive Heart Failure.* J. Cardiovasc. Pharmacol. 1991; 18 (4); 12-16; (Appendix "A" – 1991.1)

vii) Hamburger, S.A., *Carvedilol (Kredex) Reduces Infarct Size in a Canine Model of Acute Myocardial Infarction.* Pharmacology, 1991; 43 (4): 113-20; (Appendix "A" – 1991.3)

viii) Ruffolo *et al.*, Carvedilol (Kredex): *A Novel Multiple Action Cardiovascular Agent.* Drugs of Today (1991) 27 (7): 465-492; (Appendix "A" – 1991.5)

ix) DRUGS OF CHOICE, The Medical Letter on Drugs and Therapeutics, p. 85 and references cited therein; ("Beta-Blocker") (Appendix "B" No. 7)

x) *Controlled Clinical Trials in Heart Failure: Beta Blockers*, J. Am. Co. Cardiology (1993) 21 (2): Abstracts 725-1 & -2: Krum, H. *et al.*, Double-Blind, Placebo-Controlled Study of the Long-Term Efficacy of Carvedilol in Patients with Severe Heart Failure Treated with Converting-Enzyme Inhibitor. J. Am. Coll. Cardiology (1993) 21 (2): 114A abstract 725-1; Olsen *et al.*, Carvedilol Improves Symptoms and Left Ventricular Function in Patients with Congestive Heart Failure Due to Ischemic or Idiopathic Dilated Cardiomyopathy. J. Am. Coll. Cardiology (1993) 21 (2): 114A abstract 725-2; (Appendix "A"- 1993.8 and 12)

xi) Das Gupta, P. *et al., Value of Carvedilol in Congestive Heart Failure Secondary to Coronary Artery Disease*, Am. J. Cardiol. (1990) 66 (15):1118-1123; (Appendix "A" – 1990.1)

xii) Metra, M. *et al., Effects of Short- and Long-Term Carvedilol Administration on Rest and Exercise Hemodynamic Variables, Exercise Capacity and Clinical Conditions in Patients with Idiopathic Dilated Cardiomyopathy*; JACC Vol. 24, No. 7; December, 1994. (Appendix "B" No. 24)

13. I have been advised by Ogilvy Renault that, in order for a prior publication to be considered anticipatory by the Court, that single publication must contain so clear a direction that a skilled person reading and following it would be led in every case and without possibility of error to the claimed invention.

14. With respect to anticipation, I have been asked by Ogilvy Renault to consider each of the references set out in the letter of Heenan Blaikie dated February 18, 2002 as listed above and to comment on whether any of these articles may be considered anticipatory (as defined above) of the subject-matter of the '548 Patent.

15. I have also been advised by Ogilvy Renault that the Court will only consider, on the question of anticipation, documents which have been made available to the public prior to February 8, 1995.

Obviousness

16. In the Notice of Allegation, Novopharm alleges that the subject matter covered by the claims of the '548 Patent is obvious as follows:

> The subject matter covered by claims 1-52 is obvious, having regard to the prior art references listed in Appendix 'A' and the supplementary references in Appendix 'B' and the common general knowledge of a person skilled in the art on the material date, namely, the date of publication of the patent: *Whirlpool Corp.* v. *Camco Inc.* (2001) 9 CPR (4th) (S.C.C.) 129-135. Without limiting the foregoing, the following was known to the persons skilled in the art prior to February 7, 1995:
>
> [This is then followed by points (a) to (n) referring to publications in Appendices A and B, which I will discuss below]

17. I have been advised by counsel for the Applicants, and do verily believe, that the Court will only consider those references that were made available to the public prior to February 8, 1995 when determining the issue of obviousness. I have therefore been asked to provide commentary on whether:

- the publications listed at paragraphs (a) to (n) on pages 5 and 6 of the NOA; and
- the publications contained in Appendices A and B of the NOA that predate February 8, 1995,

render the subject matter of the '548 Patent obvious to a person skilled in the art. The person skilled in the art in the context of the '548 Patent is a practicing cardiologist.

18. My comments with respect to the Novopharm allegation that the subject matter covered by the claims of the '548 Patent is both anticipated and obvious is therefore limited to the references cited in the NOA that were made available to the public prior to February 8, 1995, my knowledge as a clinician and researcher in the field of cardiology since 1989 and the additional references attached hereto.

IV. SUMMARY OF OPINION

19. In my opinion, the use of carvedilol for the treatment of CHF was not known to cardiologists prior to February 8, 1995. Similarly the use of carvedilol to reduce mortality in patients suffering from CHF was not known to cardiologists prior to February 8, 1995.

20. Therefore in my opinion, the Novopharm allegation that the subject matter of the '548 Patent was known and available to the public prior to February 8, 1995 is not correct.

Furthermore, in my opinion the Novopharm allegation that the subject matter covered by the '548 Patent would have been obvious to a person skilled in the art, namely practicing cardiologists, prior to February 8, 1995, is not correct.

V. DESCRIPTION OF CARVEDILOL

21. Carvedilol is a multiaction adrenoreceptor blocking agent ("Adrenoreceptor Blocker") that provides non-selective beta-adrenergic blocking activity (i.e., blocks beta-1 and beta-2 adrenoreceptors), and also has alpha-1 adrenoreceptor blocking activity. Other Adrenoreceptor Blockers include agents that block only beta-2 and/or beta-1 receptors and agents that block alpha-1 receptors. Adrenoreceptor Blockers, as a class, act by antagonizing the effect of the sympathetic nervous system and in particular the effect of epinephrine and norepinephrine on adrenoreceptors in the heart, blood vessels, kidneys and lungs.

22. The majority of Adrenoreceptor Blockers that have been developed block either beta-2 and/or beta-1 receptors alone, or are selective for the beta-1 receptor. There are also agents that block the alpha-1 receptor alone. Carvedilol is unique in that it blocks both beta- and alpha-receptors in a single molecule, as well as uniquely providing antioxidant activity because of the carbazole moiety of its chemical structure.

23. As discussed in further detail below, carvedilol was originally used in the treatment of hypertension. It was subsequently found to be effective in the symptomatic treatment of CHF, and to increase survival in patients suffering from CHF.

VI. HYPERTENSION

A. What is Hypertension?

24. Hypertension, or high blood pressure, is a disorder characterized by the presence of consistently elevated systolic or diastolic blood pressure, which is a measure of the resistance to the flow of blood through the vessels from the heart. Hypertension is a known risk factor for stroke and myocardial infarction (heart attack) and its control has been a major goal for the prevention of these events.

B. Treatment of Hypertension

25. In order to reduce the blood pressure in hypertensive patients, typical treatments included the administration of diuretics, vasodilators, and angiotensin-converting enzyme inhibitors ("ACE inhibitors"). Diuretics eliminate salt and water thus reducing the fluid volume that must flow through the heart and blood vessels. Vasodilators increase the diameter of the blood vessels thus allowing increased ease of blood flow and ACE inhibitors block the creation of a peptide responsible for increasing blood pressure.

C. Use of Beta-blockers to Treat Hypertension

26. Beta-blockers were originally developed for the treatment of heart rhythm problems and angina pectoris. They were originally introduced in the late 1960's. By slowing heart rate and the force of contraction, they were demonstrated to reduce the oxygen demand of the heart during exercise and thus to reduce symptom-limited angina.

27. Beta-blockers were first suggested as a treatment for hypertension in the mid-1970's. This came about from clinical observations of patients treated for angina, in whom it was noted that blood pressure was lowered with chronic administration. The reduction in blood pressure may be due in part to a reduction in heart rate and the force of cardiac contraction, but it remains to this day not completely clear how the drugs work for this indication.

28. The prevailing dogma throughout the 1980's and 1990's was that beta-blockers were contra-indicated for the treatment of CHF. This was based on the concept that it would be detrimental to interfere with the sympathetic nervous system in patients with CHF who were thought to need this system to actively support their cardiac function. This was supported by early clinical experience whereby patients with angina who also had CHF were given beta-blockers and clinically worsened.

D. Use of Carvedilol to Treat Hypertension

29. Carvedilol was initially developed for hypertension based upon its combined beta-blocking and alpha-blocking activity (since both pharmocologic properties were know to provide antihypertensive effects) by Boehringer Mannheim in the 1970s and '80s.

Carvedilol received its first approval for use in hypertension in Germany in 1991 and subsequently received approval worldwide for this indication.

VII. CONGESTIVE HEART FAILURE (CHF)

A. What is Congestive Heart Failure?

30. Congestive Heart Failure ("CHF") is a clinical description of the inability of the heart to deliver sufficient oxygen to meet the body's needs. Under normal conditions, the heart acts as an effective pump delivering oxygenated blood to the body via the arteries, and collecting de-oxygenated blood via the veins. A person with damage to the heart that reduces its pumping ability is unable to deliver sufficient oxygenated blood to carry out the body's functions and is said to suffer from CHF.

31. Such damage, or inability to deliver the required oxygen to the body's tissues, may result from a number of conditions. The most common cause or etiology of heart failure is coronary heart disease. Coronary heart disease or coronary artery disease is a condition in which one or more of the large arteries that feed the heart become blocked either partially or totally. The usual way in which heart muscle is damaged from coronary artery disease is by the occurrence of one or more heart attacks or myocardial infarctions, in which one or more arteries become completely blocked and the heart muscle that is fed by a particular artery dies.

32. The other most common category of causes for heart failure is termed "idiopathic". Patients with idiopathic cardiomyopathy (cardiomyopathy simply means heart muscle disease), do not have coronary disease and may not have an easily identifiable cause for their heart muscle damage. Such damage may have occurred as the result of an exposure to a toxin, a viral infection or alcohol abuse.

33. Hypertension and CHF are two distinct medical conditions, and the principles and goals of treatment of these two medical conditions are also distinct.

B. Symptomatic Treatment of Congestive Heart Failure

(i) Clinical Endpoints and Exercise Tolerance

34. Patients suffering from CHF present with numerous symptoms, most characteristically including fatigue and weakness when performing physical activities, shortness of breath with exertion or at rest, and swelling in the extremities (edema).

35. The effect of a drug on various pressures and flows (hemodynamics) and on the clinical status in patients with heart failure is routinely assessed by testing endpoints such as ejection fraction and cardiac output ("Hemodynamic Factors"), symptom scores, quality of life instruments, global assessments of clinical status, and New York Heart Association classification ("Clinical Status").

36. Because the assessment of Hemodynamic Factors and Clinical Status (collectively "Clinical Endpoints") can be subject to bias even in blinded clinical trials, a more objective assessment of clinical benefit in heart failure was sought. "Exercise Tolerance", which includes maximal exercise testing, and submaximal exercise testing, was adopted in heart failure clinical trials as a way of more objectively assessing symptomatic improvement with less variability.

37. In summary, the assessment of symptomatic improvement for the development of most drugs is principally based on statistically significant improvements in Exercise Tolerance. Those studies that measure only Clinical Endpoints are therefore of limited use in evaluating a drug treatment or therapy for patients suffering from CHF.

38. Therefore, a cardiologist in February, 1995 would have viewed an academic writing that measured only "Clinical Endpoints" and not "Exercise Tolerance" to be of limited use in evaluating a new drug for patients suffering from CHF.

39. Prior to February 1995, traditional treatments for CHF included the use of diuretics, cardiac glycosides, vasodilators and ACE inhibitors. Each of these treatments is described in further detail below.

(ii) **Diuretics**

40. Diuretics such as furosemide (Lasix), bumetanide (Bumex), and torsemide (Demadex) reduce the amount of fluid and salt retained by the body. Such agents interfere with the sodium retention in patients with heart failure by inhibiting the reabsorption of sodium or chloride at specific sites in the kidney. Controlled trials have demonstrated the ability of diuretic drugs to decrease physical signs of fluid retention in patients with CHF within days of initiation of therapy. In intermediate-term studies, diuretics have been shown to improve Clinical Endpoints and Exercise Tolerance in patients with CHF. There have been no long-term studies of diuretic therapy in CHF and thus, their effects on morbidity and mortality are not known.

(iii) **Cardiac glycosides**

41. Cardiac Glycosides such as digoxin, beta-methyl-digoxin and digitoxin exert their effects in patients with CHF by virtue of their ability to inhibit a key enzyme called sodium-potassium (Na^+-K^+) adenosine triphosphatase (ATPase). Inhibition of this enzyme in cardiac cells results in an increase in the contractile state of the heart (positive inotropic effect), and for many decades, the benefits of digitalis in CHF were ascribed exclusively to this positive inotropic action. Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve Clinical Endpoints and Exercise Tolerance in patients with mild to moderate CHF. However, in a long-term trial that enrolled patients who primarily had class II or III symptoms, treatment with digoxin for 2 to 5 years had no effect to reduce mortality.

(iv) **Vasodilators**

42. Vasodilators such as hydralazine and isosorbide dinitrate are used to increase the diameter and reduce the pressure in the arteries and veins. They are commonly combined because of their complementary dilating actions on peripheral blood vessels. In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality (but not hospitalizations) in patients with CHF treated with digoxin and diuretics but not an ACE inhibitor or beta-blocker. There are no

controlled experiments that combine the use of hydralazine and isosorbide dinitrate therapy with an ACE inhibitor or a beta-blocker.

(v) **Angiotensin-converting Enzyme (ACE) Inhibitors**

43. ACE Inhibitors such as captopril, lisinopril, fosinopril and enalapril are also used in the treatment of CHF. These inhibitors block the conversion of Angiotensin I (a natural substance found in the body) to Angiotensin II. Angiotensin II normally causes blood vessels to constrict (narrow). ACE Inhibitors decrease the amount of Angiotensin II and reduce the constriction of the blood vessels, allowing increased blood flow and a decrease in the force with which the heart is required to pump. ACE Inhibitors alter the levels of some of the hormones in the body, in a way that is considered beneficial to the patient with heart failure.

(vi) **Beta-Blockers Contra-indicated**

44. Beta blocking agents were introduced several decades ago, originally for the treatment of arrhythmias and angina and then for hypertension. They were contra-indicated in patients with heart failure until about 1997.

45. This contra-indication was due to the fact that the compensatory activation of the sympathetic nervous system in a patient with heart failure, which is the short term attempt by the body to support the failing circulation by increasing blood pressure and heart rate, was thought to be so essential that blocking it could result in significant clinical deterioration or even death for the patient with heart failure. In fact, early reports suggested clinical deterioration of patients suffering from heart failure who were tested with beta blockers such as propranolol.

C. Reducing Mortality in CHF

(i) No Relationship Between Symptomatic Treatment of CHF and Reduced Mortality

a. V-HeFT I Trial

46. There are numerous examples of pharmacologic treatments for heart failure that improved symptoms but were not shown to reduce mortality. One of the earliest examples of this was prazosin, an alpha-1 adrenergic receptor blocker which improved hemodynamics and symptoms but in the V-HeFT I trial was shown not to improve mortality (Loeb, 1993). Attached to my affidavit as **Exhibit "G"** is a copy of the published results of Loeb, 1993.

b. Milrinone

47. Milrinone, belonging to a class of agents referred to as positive 'inotropic' drugs (because they increase the force of the contraction of the heart and the ejection fraction), initially was reported in a trial of about 200 patients to significantly increase Exercise Tolerance and reduce the frequency of worsening heart failure over 12 weeks (DiBianco, NEJM 1989). However, despite its beneficial hemodynamic actions, this same agent was subsequently shown in a long-term trial (PROMISE) of over 1000 patients to significantly increase mortality as well as hospitalizations and other serious adverse cardiovascular reaction. (Packer, NEJM 1991). Attached as **Exhibit "H"** to my affidavit is a copy of DiBianco, 1989. Attached as **Exhibit "I"** to my affidavit is a copy of Packer, 1991.

c. Flosequinan

48. Flosequinan, a direct-acting vasodilator with mild chronotropic and inotropic effects as well, is another agent that produced short and medium term benefit (up to 3 months) on hemodynamics, exercise tolerance and heart failure symptoms. However, the survival study that was performed (PROFILE) was terminated prematurely because long-term administration of the drug was associated with excess mortality.

d. Vesnarinone

49. Similarly, vesnarinone, another positive inotropic agent with a different mechanism of action, had been shown to improve Hemodynamic Factors, Exercise Tolerance and quality of life in heart failure patients, but was shown to significantly worsen mortality when used in higher doses in a larger longer-term trial (Feldman, 1993). Attached as **Exhibit "J"** is a copy of the publication by Feldman, 1993.

50. As a result of the studies described above, it was clear to cardiologists prior to February 8, 1995 that drugs that resulted in an improvement in Clinical Endpoints would not necessarily improve survival. In fact, some drugs that improved Clinical Endpoints resulted in an increase in mortality.

(ii) ACE Inhibitors

51. Prior to February 1995, the only class of drugs used in the treatment of CHF that demonstrated efficacy in treating both symptomatic CHF and a reduction in mortality was ACE inhibitors. Enalapril and captopril are the two agents that were initially recommended for use in CHF, but subsequently the indication was broadened to include other ACE inhibitors.

(iii) Beta Blockers

52. As discussed above, clinical management of CHF has typically focused on the management of the patient's symptoms. Clinical research has demonstrated that symptomatic improvement does not predict the effect of the treatment on mortality. This was discussed above for non-beta blocking agents and will be discussed below for beta blockers.

53. Prior to February 1995, there were only three reported large scale, randomized double blind studies measuring the effect of Beta-blockers on mortality. These were as follows:

(i) Xamoterol Trial [Lancet 1990, Vol: 336 1-6]

(ii) MDC Trial [Lancet, 1993 Vol 342] and

(iii) CIBIS I Trial [Circulation 1994].

Attached as **Exhibit "K", "L"**, and **"M"** are copies of the published papers reporting the results of the Xamoterol Trial, the MDC Trial and the CIBIS I Trial.

54. The above named studies were all randomized, double blind, placebo controlled studies with significant sample size. It is important to rely only upon such studies to inform clinical practice because of the concern that smaller studies do not provide reliable signals for providing safe and effective symptomatic treatment or mortality improvement. Hence, any study that does not fall into this category would not be regarded by cardiologists as anything more than a signal requiring further study. Because signals in such studies may or may not be confirmed by later large-scale testing, it is generally the case that smaller initial studies do not result in a change in clinical practice.

a. The Xamoterol Study

55. Xamoterol was the first agent with beta-blocking activity approved for the use in heart failure. Although xamoterol also has intrinsic sympathomimetic activity, it was originally approved for the symptomatic improvement of heart failure and subsequently shown to worsen survival in patients with severe heart failure. In fact, that trial was stopped early by its Data and Safety Monitoring Board because of harm to patients. This result provided additional concern about the safety and tolerability of beta-blockade in CHF patients.

b. The MDC Trial

56. The MDC Trial was also a randomized, double blind, placebo controlled study, involving 383 patients published in 1993. This study examined the effect of the Beta-blocker metoprolol on either the mortality of patients, or the patients' deterioration to the point of requiring a heart transplant. A secondary objective was to determine the effect of metoprolol on Clinical Endpoints and Exercise Tolerance. The study determined that metoprolol had no effect on mortality although there was a demonstrable improvement in Exercise Tolerance and cardiac function. In fact, there were slightly more deaths in patients randomized to metoprolol as compared with placebo.

c. CIBIS I Study

57. The CIBIS I study was a randomized, double blind, placebo controlled study of 641 patients published in 1994. This study was designed to determine the effect of bisoprolol on mortality. Bisoprolol is a Beta-1 selective adrenergic blocking agent. Based on the results of this study, the authors were unable to demonstrate a statistically significant reduction in mortality after treatment with bisoprolol over a two-year time period.

58. These studies did nothing to reverse the prevailing sentiment through February 8, 1995 that agents with beta-blocking activity did not improve survival in heart failure patients and even suggested that beta-blockers would increase this risk. Practicing cardiologists continued to consider beta blockers as contra-indicated in patients with heart failure.

VIII. DEVELOPMENT OF CARVEDILOL BY GSK

A. Re-Evaluation of Beta-Blockers for Treatment of CHF

59. In the late 1980's, early 1990's, clinical researchers were re-evaluating their thinking with respect to the potential use of Beta-blockers in treating CHF. Although prior to this time, Beta-blockers were considered contra-indicated, interest in the use of Beta-blockers had been triggered by the small, inconclusive preliminary studies suggesting that such drugs might be beneficial in treating the symptoms of CHF.

60. Although these studies were important in suggesting that perhaps some Beta-blockers might be worth testing for use in CHF, they were in no way sufficient to change the thinking of practicing clinicians when presented with a patient with CHF. This is particularly true given the general dogma that Beta-blockers were considered contra-indicated for patients with CHF.

B. The GSK Carvedilol Study

61. GSK designed the U.S. Carvedilol Trials Program (the "GSK Carvedilol Study") to test the potential of carvedilol to effect the clinical status/symptomatic status of patients with CHF. The GSK Carvedilol Study was designed to determine as primary endpoints the evaluation of sub maximal exercise by the six minute walk test and the nine minute self-

powered treadmill walk. This study was published on May 23, 1996 in the New England Journal of Medicine. Attached as **Exhibit "N"** to my affidavit is a copy of the publication of the GSK Carvedilol Study.

62. Although the GSK Carvedilol Study was designed to determine the effect of carvedilol on Clinical Endpoints and Exercise Tolerance, given the Xamoterol, MDC and CIBIS I studies described above, GSK was concerned about the possibility of carvedilol causing an increase in the mortality of patients. As such, the decision was made to utilize an independent Data Safety Monitoring Board ("DSMB") to monitor the effect of carvedilol on mortality to determine if patient safety was being compromised.

63. The DSMB for the U.S. Carvedilol Trials consisted of three cardiology opinion leaders and a biostatistician and their mandate was to monitor and protect the safety of the patients in the trials specifically with respect to the incidence of mortality and worsening heart failure. They were supplied with blinded data on a prespecified basis for review. They met periodically as required by the data and were actioned to inform the company if a significant safety concern arose during the study.

64. Despite our concerns regarding the possibility of increased mortality by treatment with carvedilol, our study demonstrated the surprising result of a 65% decrease in the risk of mortality. This effect was larger than that seen with ACE inhibitors and suggested a very powerful, beneficial effect of carvedilol for treatment of patients with CHF.

65. As a result of these encouraging and unexpected results, the DSMB halted the study prematurely in February 1995, despite the designed end date of the study which was to be late in 1995 or early 1996. The DSMB felt that the results they saw were such that placebo patients should no longer be denied carvedilol. They not only stopped the study early, but actively recommended that all patients on the placebo arm of the study be offered the active drug.

C. Filing of '548 Patent

66. As a result of the unexpected results, the German Patent Application was filed on February 8, 1995 on behalf of the Boehringer Mannheim Pharmaceuticals Corporation –

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SmithKline Beecham Corporation Limited Partnership (the "Limited Partnership") disclosing the use of carvedilol for both the treatment of CHF and the use of carvedilol for the reduction of mortality in patients with CHF.

D. Mortality Claims Require Further Study

67. Despite these significant findings, there were many within the scientific community that expressed skepticism about utilizing carvedilol in the treatment of patients with CHF. Concerns expressed included the fact that the GSK Carvedilol Study was not originally designed to test the endpoint of mortality, and therefore some felt that these findings could not be relied upon. In addition, the GSK Carvedilol Study enrolled primarily patients with mild to moderate (i.e., NYHA Class II-III) CHF and the concern remained that patients with more severe forms of CHF would be harmed by treatment with carvedilol long before any beneficial effects would be realized.

68. A prominent example of these concerns is expressed in an editorial written by Marc Pfeffer and Lynn Warner Stevenson, published concomitantly with our study in the New England Journal of Medicine on May 23, 1996. The editorial states as follows:

- '...the combined experience with carvedilol gives a tantalizing hint that the risk of death in patients with heart failure may be reduced by this beta-blocker."
- "Studies of beta-blockers...have shown improved left ventricular ejection fraction and fewer hospitalizations. The translation of these benefits into improved survival can no longer be assumed."
- "Although the carvedilol study adds considerable momentum to the ongoing efforts to demonstrate the usefulness in heart failure, its promising results are not sufficient for us to conclude that they improve survival."
- "The patients with heart failure for whom physicians are most likely to seek additional therapy are those with severe symptoms, but these patients were the least well represented in the study...constituting only 3 percent of the entire study population. Because of the truncation of follow-up, even among the 105 patients designated as having 'severe' heart failure, there were only four deaths. This study neither supports nor advocates the administration of beta-blockers to patients with severe heart failure".

Attached as **Exhibit "O"** to my affidavit is a copy of the Pfeffer editorial.

E. Second GlaxoSmithKline Inc. Carvedilol Trial - COPERNICUS

69. In order to address the concerns described above, GSK sponsored the Carvedilol Prospective Randomized Cumulative Survival Study (the "COPERNICUS Study"). This study was specifically designed to test the endpoint of mortality, including the effectiveness of treating patients presenting with more severe forms of CHF using carvedilol.

70. In the COPERNICUS Study, 2289 patients with symptoms of heart failure at rest or on minimal exertion and a left ventricular ejection fraction ("LVEF") of less than 25% were randomly assigned to double-blind treatment with placebo (n=1133) or carvedilol (n=1156) for a mean of 10.5 months, while background therapy was continued. By intention-to-treat, carvedilol therapy was associated with a 35% decrease in the risk of death (P=0.00013). Carvedilol also significantly reduced the combined risk of death or hospitalization for any reason by 24% (P=0.00004), of death or hospitalization for a cardiovascular reason by 27% (P=0.000023), and of death or hospitalization for heart failure by 31% (P=0.000004). These benefits were apparent and consistent regardless of age, gender, cause of heart failure, LVEF or a recent or recurrent history of cardiac decompensation.

71. The COPERNICUS study enrolled patients whose heart failure was more advanced than those enrolled in the GSK Carvedilol Study. Previous work had raised important questions about both the efficacy and safety of β-blockade in such severe degrees of heart failure; yet, carvedilol was effective and well-tolerated overall and among those patients at highest risk. Attached as **Exhibit "P"** to my affidavit is a copy of the COPERNICUS study published in the New England Journal of Medicine.

72. The result of the COPERNICUS study extended the highly favorable benefit-to-risk relation previously reported with carvedilol in patients with mild-to-moderate heart failure to those with severe heart failure. This was a significant finding.

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IX. ANTICIPATION

73. I am advised by counsel for Ogilvy Renault that in order for a prior publication to be considered anticipatory, that publication must contain so clear a direction that a skilled person reading and following it would be led in every case and without possibility of error to the claimed invention.

74. I have been advised by Ogilvy Renault that Novopharm has identified, through a letter of its attorneys Heenan Blaikie dated February 18, 2002, the references from Appendices A and B on which Novopharm relies in support of its allegation of anticipation.

75. I have considered each of the references referred to in relation to the '548 Patent cited in the letter of Heenan Blaikie dated February 18, 2002. For the reasons set out in my specific comments, I consider that none of these publications contain so clear a direction that a skilled person reading and following it would be led in every case and without possibility of error to the claimed invention of the '548 Patent.

76. Each of the prior art documents referred to in my affidavit contains a Tab reference that corresponds to the documents attached as Exhibit "F" to the Affidavit of Patricia N. Jansons sworn March 4, 2002. For example, a reference to Tab 1 in this affidavit refers to the document contained at Tab "F" – 1 of the Jansons Affidavit.

77. Specific comments with respect to each of the 12 points raised by Novopharm in the February 18, 2002 letter of Heenan Blaikie are as follows:

Point i)

i) Senior, R. et al., *Effects of Carvedilol on Ventricular Arrhythmias*; J. Cardiovasc. Pharmacol., Vol. 19 (Suppl. 1), 1992; (Appendix "A" – 1992.7)

Reference: Jansons Affidavit – Tab 27

78. This paper is not a randomized, double blind, placebo controlled study and only 12 of the 65 enrolled patients even presented with CHF. Furthermore, the stated purpose of the study was to determine the anti-arrhythmic effect of carvedilol. Prior studies, (for example, the CAST study in 1989 (NEJM 321(6) 406-412) have made it clear that there

is no recognized link between anti-arrhythmic effects and mortality. In fact, certain anti-arrhythmic drugs increase mortality. The Senior, 1992 paper does not look at whether carvedilol is helpful in affecting the Exercise Tolerance of patients and thus does not teach the use of carvedilol in the treatment of CHF. The use of carvedilol for the reduction of mortality in patients suffering from CHF is not discussed.

Point ii)

ii) Kelly, D.T.; *Carvedilol in Heart Failure*; Cardiology 1993; 82 (suppl. 3):45-49; (Appendix "A" – 1993.7)

Reference: Jansons Affidavit – Tab 33

79. The Kelly paper is a summary article that states that carvedilol improves hemodynamics in patients with CHF, and refers to Das Gupta for this point. Studies that measure Clinical Endpoints other than Exercise Tolerance, while of interest, do not provide any teaching to cardiologists with regards to the use of carvedilol for the treatment of CHF. (See: Discussion of Clinical Endpoints and Exercise Tolerance above.) This paper admits the need for a large scale, randomized, placebo controlled study to determine whether carvedilol may be useful for treatment of CHF.

Point iii)

iii) Ohlstein, E., United States Patent No. 5,308,862 issued May 3, 1994 based on Application No. 26,892 filed March 5, 1993 for an invention entitled USE AND METHOD OF TREATMENT USING CARBAZOLYL-(4)-OXYPROPANOLAMINE COMPOUNDS FOR INHIBITION OF SMOOTH MUSCLE CELL PROLIFERATION; (Appendix "A" – 1994.9)

Reference: Jansons Affidavit – Tab 54

80. The Ohlstein patent has nothing to do with heart failure, it was filed in reference to the effects of carvedilol on smooth muscle cells as related to angioplasty. Two statements are made regarding 'utility' having been demonstrated in CHF. The references included in the patent describe the preliminary Krum and Olsen results, the deficiencies of which in this regard are discussed elsewhere.

Point iv)

iv) Appelgren *et al.*, United States Patent No. 4,888,179 issued December 19, 1989 based on Application No. 144,229 filed January 15, 1988 for an invention entitled DIURETIC COMPOSITION; (Appendix "A" – 1989.2)

Reference: Jansons Affidavit – Tab 10

81. I find no mention of carvedilol in this patent. The only reference to heart failure is regarding the usefulness of furosemide as a diuretic in this condition. Therefore, this article in no way suggests the benefit of or supports the use of carvedilol in heart failure.

Point v)

v) Finkelstein et al., United States Patent No. 5,312,823 issued May 17, 1994 based on Application No. 746,024 filed August 14, 1991 for an invention entitled SUBSTITUTED IMIDAZOLES HAVING ANGIOTENSIN II RECEPTOR BLOCKING ACTIVITY; (Appendix "A" – 1994.4)

Reference: Jansons Affidavit – Tab 55

82. This patent merely states that ACE inhibitors are useful in the treatment of CHF. This does not suggest any combination with carvedilol for either symptomatic treatment of CHF or the reduction of mortality in patients suffering from CHF.

Point vi)

vi) Das Gupta, P. *et al.*, *The Effects of Intravenous Carvedilol, a New Multiple Action Vasodilatory Beta-Blocker, in Congestive Heart Failure.* J. Cardiovasc. Pharmacol. 1991; 18 (4); 12-16; (Appendix "A" – 1991.1)

Reference: Jansons Affidavit – Tab 18

83. This paper recognizes the limitations in Das Gupta's previous work. The study again only tests 17 patients and examines the immediate effects of carvedilol after 10 to 30 minutes. This study does not even address Exercise Tolerance, and some of the other end points tested are admitted by the author to be of no statistical significance. In addition, this article deals with intravenous carvedilol. The effects of a single dose administration of intravenous carvedilol, particularly because of the stereoselective metabolism of the drug, are irrelevant to describing its chronic effects in heart failure patients.

Point vii)

vii) Hamburger, S.A., *Carvedilol (Kredex) Reduces Infarct Size in a Canine Model of Acute Myocardial Infarction*. Pharmacology, 1991; 43 (4): 113-20; (Appendix "A" – 1991.3)

Reference: Jansons Affidavit – Tab 16

84. This article is the report of a preclinical (in dogs) investigation of the effect of carvedilol on myocardial infarction size, which showed that the drug could markedly decrease infarct size in this model. The authors merely postulate that this effect may contribute to the potential use of the drug in angina or heart failure, and point out that clinical trials were underway to establish its utility in heart failure. Therefore, the article in no way teaches the use of carvedilol in heart failure.

Point viii)

viii) Ruffolo *et al.*, Carvedilol (Kredex): *A Novel Multiple Action Cardiovascular Agent*. Drugs of Today (1991) 27 (7): 465-492; (Appendix "A" – 1991.5)

Reference: Jansons Affidavit – Tab 17

85. This is a general review article on carvedilol's pharmacology and clinical trial database (efficacy and safety). It specifically mentions only that carvedilol had potential to be effective in heart failure, that clinical trials were at the time in progress to establish its utility in heart failure, and that its multiple actions might ultimately prove to be beneficial in heart failure therapy. In the section relating to heart failure, only the rationale for benefit is discussed, and the early, preliminary data from Das Gupta *et al.* are reviewed. The severe limitations of the data in these references in this regard have been discussed elsewhere in this affidavit. References on data on other beta-blockers in heart failure are mentioned in summary, all of which are either small in patient number, inadequately controlled, or short in duration. For all of these reasons, this article does not inform or teach about the use of carvedilol in heart failure.

Point ix)

ix) DRUGS OF CHOICE, The Medical Letter on Drugs and Therapeutics, p. 85 and references cited therein; ("Beta-Blocker") (Appendix "B" No. 7)

Reference: Jansons Affidavit – Tab 37

86. What was provided is an exerpt from a medical letter entitled, "Beta-blocker. Drugs of choice." The selected text describing beta-blockers is a summary statement that preliminary controlled trials with metoprolol, carvedilol and bucindolol had indicated improvement in symptoms and LV function in heart failure patients with idiopathic cardiomyopathy. However the piece does not describe effects of the drug on exercise or mortality and it has previously been stated that symptoms and left ventricular function are not adequate to establish the benefit of a drug in patients with heart failure. The medical letter selection goes on to state importantly that the effect of the drugs in heart failure patients in coronary artery disease had not been adequately evaluated. Since this is such a large part of the population it is a further reason why this piece cannot be considered to teach or inform about the use of the drug in heart failure patients.

Point x)

x) *Controlled Clinical Trials in Heart Failure: Beta Blockers*, J. Am. Co. Cardiology (1993) 21 (2): Abstracts 725-1 & -2:

- Krum, H. *et al.*, Double-Blind, Placebo-Controlled Study of the Long-Term Efficacy of Carvedilol in Patients with Severe Heart Failure Treated with Converting-Enzyme Inhibitor. J. Am. Coll. Cardiology (1993) 21 (2): 114A abstract 725-1;

- Olsen *et al.*, Carvedilol Improves Symptoms and Left Ventricular Function in Patients with Congestive Heart Failure Due to Ischemic or Idiopathic Dilated Cardiomyopathy. J. Am. Coll. Cardiology (1993) 21 (2): 114A abstract 725-2;

(Appendix "A"- 1993.8 and 12)

Reference: Jansons Affidavit – Tab 41

87. The study by Krum was a pilot evaluation of the effects of carvedilol, in combination with other drugs, and as such only looks at 32 patients with CHF, which is much too small a number of patients upon which to base a decision as to the sustained effect of the

drug on Exercise Tolerance. This study is merely preliminary and does not teach cardiologists that carvedilol can be used for the treatment of CHF. Similarly, the Olsen study only looks at 54 patients and then only reports on the effects of the drug on Clinical Endpoints and not Exercise Tolerance.

Point xi)

xi) Das Gupta, P. *et al., Value of Carvedilol in Congestive Heart Failure Secondary to Coronary Artery Disease*, Am. J. Cardiol. (1990) 66 (15):1118-1123; (Appendix "A" – 1990.1)

Reference: Jansons Affidavit – Tab 15

88. This paper by Das Gupta is reviewed below under obviousness, and the comments apply here to anticipation as well.

Point xii)

xii) Metra, M. *et al., Effects of Short- and Long-Term Carvedilol Administration on Rest and Exercise Hemodynamic Variables, Exercise Capacity and Clinical Conditions in Patients with Idiopathic Dilated Cardiomyopathy*; JACC Vol. 24, No. 7; December, 1994. (Appendix "B" No. 24)

Reference: Jansons Affidavit – Tab 58

89. The Metra paper studied the effects of the drug on a variety of clinical variables in a small number of patients (40) without a pre-determined statistical rationale or sample size calculation and thus cannot be considered to provide definitive evidence of the effect of carvedilol on Exercise Tolerance. This reference would not teach a practicing cardiologist anything about the use of carvedilol for the treatment of CHF or reduction of mortality in patients suffering from CHF.

X. OBVIOUSNESS

90. I have been advised by Ogilvy Renault and do verily believe that the Court will only consider the issue of obviousness on the basis of references that were made available to the public prior to February 8, 1995. I will therefore only provide commentary on those documents in the Notice of Allegation that were made available to the public prior to that date.

91. I have been further advised by Ogilvy Renault that a patent may be considered obvious by the Court where references published prior to the filing date of the patent would lead a person skilled in the art directly and without difficulty to the solution or invention taught by the patent.

92. I have been asked by Ogilvy Renault to comment on whether the subject matter of the '548 Patent was obvious to a person skilled in the art, in this case a practicing cardiologist, as of February 8, 1995. I have also been asked to: (i) comment upon the statements made under the subheading of "Obviousness" in paragraphs (a) to (n) on pages 5 and 6 of the Notice of Allegation, and (ii) to provide commentary on the remaining pieces of prior art listed in Appendices A and B to the NOA.

93. Before I comment on the specific prior art references in the Novopharm Notice of Allegation, I believe that it is important to understand that, in order for the medical community to accept a new drug for the treatment of heart conditions such as CHF, the drug must be tested in a large scale, randomized, double blind, placebo controlled trial. Many drugs have suggested promise in early investigatory studies, which when subjected to the rigorous standards of a proper trial have been proven harmful (for example, xamoterol and bucindolol).

94. Many of the prior art references in the NOA are examples of such preliminary, investigatory studies that suggest that carvedilol might be beneficial in the treatment of CHF. These studies, while interesting, were small in number and dealt with a very limited number of patients. They do nothing more than suggest that carvedilol might be worth further investigation.

Points (a) to (n) in the Notice of Allegation

95. Specific comments with respect to each of the 14 points raised by Novopharm on pages 5 and 6 of the Notice of Allegation are provided below. In summary, none of the references cited below, for the reasons provided, would have led a practicing cardiologist directly and without difficulty to the solution or invention taught by the '548 Patent.

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Points (a) and (b)

(a) Beta blockers (metoprolol) used with digitalis and diuretics to treat congestive cardiomyopathy. (Swedberg, 1979);

(b) early tests with beta blockers suggested that they would prolong survival in patients with CHF. (Swedberg, 1979);

Reference: Jansons Affidavit – Tab 2

Swedberg, K. et al., *Prolongation of Survival in Congestive Cardiomyopathy by Beta-Receptor Blockade* Lancet, June 30, 1979: 1374-1376.

96. The Swedberg study did not test carvedilol but reported on the effects of metoprolol, practolol, and alprenolol. This study is fatally flawed in that it was not a randomized, double blind, placebo controlled study and furthermore utilized a retrospective analysis of past patients. Furthermore, results obtained with early generation Beta-blockers are not indicative of results with carvedilol which has multiple modes of action.

Point (c)

(c) Beta blockers have negative inotropic effects (weakening of muscle). Carvedilol does not have negative inotropic effects because of its ?- and ?-blocking properties. Hence, carvedilol may have beneficial effects for patients with chronic CHF secondary to coronary artery disease (Das Gupta, 1990);

Reference: Jansons Affidavit – Tab 15

Das Gupta, P. et al., *Value of Carvedilol in Congestive Heart Failure Secondary to Coronary Artery Disease*, Am J Cardiol 1990;66:1118-1123.

97. The suggestion that carvedilol does not have a negative inotropic effect is untrue. Carvedilol has vasodilating effects, which in theory may allow the negative inotropic effect of carvedilol to be better tolerated. This hypothesis has still yet to be proven, even today, and it is not yet understood why carvedilol is useful for treatment of CHF nor is it understood why carvedilol improves the mortality in patients treated. This study tests only 17 patients and my earlier comments with respect to the limited use of such trials applies here.

Point (d)

(d) a single intravenous dose of carvedilol is safe and well-tolerated in chronic congestive heart failure of ischemic origin. Carvedilol may be expected not only to improve cardiac function by its ?-blocking properties, but also its vasodilating action may counterbalance the negative inotropism (Das Gupta, 1991);

Reference: Jansons Affidavit – Tab 18

Das Gupta, P. et al., *The Effects of Intravenous Carvedilol, A New Multiple Action Vasodilatory β-Blocker, in Congestive Heart Failure*, J Cardiovasc Pharmacol, Vol. 18 (Suppl. 4), 1991, pages S12-16.

98. This paper by Das Gupta is reviewed above under anticpation, and the comments apply here to obviousness as well.

Point (e)

(e) in the CHF group, the beneficial effects of carvedilol on left ventricular function and hemodynamics may combine with the improvement in PVC (premature ventricular contractions) activity to produce a significant improvement in mortality. (Senior, 1992);

Reference: Jansons Affidavit – Tab 27

Senior, R. et al., *Effects of Carvedilol on Ventricular Arrhythmias*. J Cardiovasc Pharmacol 19(Suppl. 1):S117-121, 1992.

99. This paper by Senior is reviewed above under anticpation, and the comments apply here to obviousness as well.

Point (f)

(f) Carvedilol may have some additional properties including improvement of left ventricular diastolic function and regression of left ventricular hypertrophy, anti-anginal and anti-arrhythmic activity and improvement of central hemodynamics in patients with congestive heart failure (i.e. dealing with the underlying causes of CHF). (Rosendorff, 1993);

[Note: left-ventricular hypertrophy has been identified in the Framingham study and in other trials as one of the most potent individual risk factors for cardiac morbidity and mortality. (Lessem, 1993)]

Reference: Jansons Affidavit – Tabs 35 and 34

Rosendorff, C. *Beta-blocking agents with vasodilator activity*, J Hypertens 1993, 11 (suppl 4):S37-40.

Lessem, J.N. and Lukas, M.A. *Development of a Multiaction Beta Blocker: Scientific Challenges and Regulatory Needs.* Cardiology 1993;82(suppl 3):50-58.

100. The Rosendorff paper is a review of previous studies and states that carvedilol may be helpful in improving left ventricular diastolic function, regression of left ventricular hypertrophy and anti-arrythmatic effects. This review also suggests that Das Gupta, 1992 demonstrates an improvement in hemodynamics. Studies that measure Clinical Endpoints other than Exercise Tolerance, while of interest, do not provide any teaching to cardiologists with regards to the use of carvedilol for the treatment of CHF.

101. The Lessem, 1993 publication, of which I am a co-author, makes reference to the fact that in the Framingham experience LVH was the most potent individual risk factor identified for cardiovascular disease progression. While this may be true, it would need to be tested and proven in a randomized placebo controlled trial that reduction of LVH is associated with reduction in mortality. In addition, LVH is a condition distinct and separate from CHF. This paper does not teach cardiologists that carvedilol can be used for the treatment of CHF or the reduction of mortality in patients suffering from CHF.

Point (g)

(g) Carvedilol was administered to patients with severe heart failure. The patients were also treated with digoxin, diuretics and ACE inhibitors. Carvedilol produced hemodynamic and clinical benefits in patients with severe CHF treated with ACE inhibitors. (Henry Krum *et al.*, 1993) Furthermore, carvedilol was well tolerated and improved both symptoms and cardiac function in patients with either ischemic or idiopathic cardiomyopathy. (Stephanie Olsen *et al.*, 1993);

Reference: Jansons Affidavit – Tab 41

Krum, H. et al., *Controlled Clinical Trials in Heart Failure I: Beta-Blockers*, JACC Vol.21, No. 2, February 1993:114A, Abstract 725-1.

Olsen, S. et al., *Carvedilol Improves Symptoms and Left Ventricular Function in Patients with Congestive Heart Failure Due to Ischemic or Idiopathic Dilated Cardiomyopathy*, JACC Vol. 21, No. 2, February 1993: 114A, Abstract 725-2.

102. These abstracts by Krum and Olsen are reviewed above under anticpation, and the comments apply here to obviousness as well.

Point (h)

> (h) studies demonstrated symptomatic improvement with carvedilol in patients with heart failure. Data from the trial suggested that carvedilol may have had beneficial effects in patients with chronic heart failure secondary to coronary artery disease. The patients in the trial were also on diuretics. A multicentre trial had been designed to see if beta blockade has the same type of effect in ischaemia as it had in cardiomyopathy. The use of ACE inhibitors was encouraged. Patients were dosed at 3.125 mg twice daily for 7 days, in the second week 6.25 mg, then 12.5 mg and the following week 25 mg twice daily, being the maximal dose (Kelly, 1993);
>
> **Reference: Jansons Affidavit – Tab 33**
>
> Kelly, D.T., *Carvedilol in Heart Failure*, Cardiology 1993;82(suppl 3):45-49.

103. This paper by Kelly is reviewed above under anticpation, and the comments apply here to obviousness as well.

Point (i)

> (i) Studies have clearly demonstrated that some patients with congestive heart failure due to idiopathic, ischaemic and other forms of cardiomyopathy improve on long term ß-blocker therapy (Hjalmarson, 1994);
>
> **Reference: Jansons Affidavit – Tab 51**
>
> Hjalmarson, A. and Waagstein, F., *The Role of ß-Blockers in the Treatment of Cardiomyopathy and Ischaemic Heart Failure*, Drugs 47 (Suppl. 4): 31-40, 1994.

104. This paper, co-authored by Waagstein, is a summary article. The article recognizes that the earlier Waagstein and Swedberg studies suggesting the Beta-blocker metoprolol might be beneficial for the improvement of mortality were skeptically received by the medical community. Even as of this late date, Hjarmalson recognizes the need to study the long term effects of Beta-blockers to determine their use in the treatment of CHF. After reviewing the pharmacokinetics of all of the potential Beta-blocker candidates,

including carvedilol, Hjarmalson proposes a large scale study with metoprolol, rather than carvedilol to determine the effectiveness in treatment of CHF.

Point (j)

(j) Carvedilol could be used to treat CHF. (Ohlstein patent, 1994);

Reference: Jansons Affidavit – Tab 54

Ohlstein, E.H., United States Patent No. 5,308,862, "*Use of, and Method of Treatment Using, Carbazolyl-(4)-Oxypropanolamine Compounds for Inhibition of Smooth Muscle Cell Proliferation*", May 3, 1994.

105. This patent by Ohlstein is reviewed above under anticpation, and the comments apply here to obviousness as well.

Point (k)

(k) ACE inhibitor, captopril, can be used in treatment of CHF. (Finkelstein patent, 1994);

Reference: Jansons Affidavit, Tab 55

Finkelstein, J.A. et al., United States Patent No. 5,312,828, "*Substituted Imidazoles Having Angiotensin II Receptor Blocking Activity*", May 17, 1994.

106. This patent by Finkelstein is reviewed above under anticpation, and the comments apply here to obviousness as well.

Point (l)

(l) Carvedilol is an important new drug in the management of CHF (along with hypertension and ischaemic heart disease) (Louis, 1994);

Reference: Jansons Affidavit – Tab 52

Louis, W.J. et al., *A Risk-Benefit Assessment of Carvedilol in the Treatment of Cardiovascular Disorders*, Drugs Safety 11(2):86-93, 1994.

107. This is a summary article that relies on Krum, 1993 and Olsen, 1993 to suggest carvedilol is useful for treatment of CHF. Such studies, that are too small to appropriately, and with sufficient statistical power, assess the Clinical Endpoints and Exercise Tolerance and do not provide any teaching to cardiologists that carvedilol can be used for the treatment of CHF.

Point (m)

> (m) activation of the sympathetic nervous system was known to be associated with progressive deterioration of cardiac function and clinical condition and increased mortality in patients with chronic congestive heart failure. Beta-adrenergic blocking agents, because of their ability to inhibit sympathoadrenergic drive, were therefore known to be potentially useful for the long-term treatment of this syndrome. The study evaluated the use of carvedilol on patients with CHF who were also treated with digoxin, diuretic agents (furosemide) and ACE inhibitors (Metra, 1994);
>
> **Reference: Jansons Affidavit – Tab 58**
>
> Metra, M. et al., *Effects of Short- and Long-Term Carvedilol Administration on Rest and Exercise Hemodynamic Variables, Exercise Capacity and Clinical Conditions in Patients with Idiopathic Dilated Cardiomyopathy*, JACC Vol. 24, No. 7, December 1994:1678-87.

108. This paper by Metra is reviewed above under anticpation, and the comments apply here to obviousness as well.

Point (n)

> (n) preliminary controlled trials with metoprolol (Lopressor) and two experimental beta-blockers, bucindolol and carvedilol, indicate that low doses of these drugs can improve symptoms and left ventricular function in patients with heart failure due to an idiopathic dilated cardiomyopathy. (The Medical Letter on Drugs and Therapeutics, Drugs of Choice, 1993 citing B. Andersson et al., J Am Coll Cardiol, 18:1059, 1991; E.M. Gilbert et al., Am J Med, 88:223, 1990; P. Das Gupta et al., Am J Cardiol, 66:1118, 1990).
>
> **Reference: Jansons Affidavit – Tab 37**
>
> Beta-Blocker. Drugs of Choice, *The Medical Letter on Drugs and Therapeutics*, 1993, p. 85.

109. This paper is reviewed above under anticpation, and the comments apply here to obviousness as well.

Reference: Jansons Affidavit – Tab 21

Anderson, B. et al., Exercise Hemodynamics and Myocardial Metabolism During Long-Term Beta-Adrenergic Blockage in Severe Heart Failure, J Am Coll Cardiol 1991;18:1059-66.

110. This article reports on an open label investigation of hemodynamics and myocardial metabolism in 21 heart failure patients receiving metoprolol. The author states that the primary objective of the study was to determine whether favorable effects on myocardial performance and metabolism at rest would be maintained during exercise. They further state that the study was inherently weak because of its open design. The results therefore cannot be considered to teach or inform about the use of beta-blocker therapy in heart failure. Carvedilol is not mentioned in the study and no effect on mortality is (or could be) assessed.

Reference: Jansons Affidavit – Tab 13

Gilbert, E.M. et al., Long-Term Beta-Blocker Vasodilator Therapy Improves Cardiac Function in Idiopathic Dilated Cardiomyopathy: A Double-Blind, Randomized Study of Bucindolol versus Placebo, Am J Med 1990;88:223-229.

111. The article provides a report of a small, short term (3 months) placebo controlled study of the beta-blocker bucindolol in patients with dilated cardiomyopathy. Carvedilol was not mentioned in the article. The authors provide data on hemodynamics and exercise testing. The authors specifically indicate that the primary objective of the study was to assess the safety and tolerability of bucindolol in this patient population and not to establish efficacy. The study was not powered to appropriately prospectively evaluate the effect of the drug on exercise testing and certainly was too small to evaluate the effect on mortality. For these reasons, this article cannot be considered to teach or inform physicians on the use of beta-blockade in heart failure. In addition it should be noted that bucindolol was subsequently shown not to provide a mortality benefit in heart failure in the BEST trial, which provides further evidence why small short term studies cannot be considered of use in the establishment of clinical efficacy.

Additional References cited at Appendices A and B to the Notice of Allegation

112. In addition to the sixteen references cited in points (a) to (n) above, Novopharm has also cited approximately 90 additional academic publications in Appendices A and B to the NOA to support its allegation that the subject matter of the '548 Patent is obvious. My comments with respect to each of those pieces of prior art that were made available to the public prior to February 8, 1995 are attached as **Exhibit "Q"** to my affidavit.

Conclusion

113. In summary, it is my opinion that none of the prior art cited above (including the prior art commented upon at Exhibit "Q") that was published prior to February 8, 1995, would have taught a cardiologist as of February 8, 1995, to use carvedilol for the treatment of CHF, or to use carvedilol to reduce mortality in patients suffering from CHF. Furthermore, none of the relevant prior art cited above taken as a whole or in combination would have made it obvious to a cardiologist as of February 8, 1995, to use carvedilol for the treatment of CHF or to use carvedilol to reduce mortality in patients suffering from CHF.

SWORN BEFORE ME at the City of Pasadena, in the State of Maryland, this 7th day of March, 2002.

A Commissioner, etc.

NOTARY PUBLIC, ANNE ARUNDEL CO., MARYLAND
MY COMMISSION EXPIRES JANUARY 1, 2004

DR. MARY ANN LUKAS

UNITED S[redacted] DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.
08/483,625			

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Prof Dr Gisbert Speyer (3) Ms. Mary McCarthy

(2) Dr rer nat Manfred Weber (4) William Jarvis

Date of interview 20 August 1996

Type: ☐ Telephonic ☑ Personal (copy is given to ☐ applicant ☑ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☑ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☑ was not reached.

Claims discussed: all

Identification of prior art discussed: Ohlstein and others

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant and his attorneys explained the difference between mortality and quality of life with regards to congestive heart failure. Applicant will submit a response shortly addressing the office action and the alleged unexpected advantage of carvedilol over the prior art.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☐ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

William R. Jarvis
Examiner's Signature

PTOL-413 (REV. 2 -93)

APPLICANT'S COPY

LEXSEE 254 F3D 1053

DAVID M. RAPOPORT, Appellant, v. WILLIAM C. DEMENT, MARK R. ROSEKIND, and JEFFREY L. SCHWIMMER, Appellees.

00-1451

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

254 F.3d 1053; 2001 U.S. App. LEXIS 14322; 59 U.S.P.Q.2D (BNA) 1215

June 28, 2001, Decided

PRIOR HISTORY: [**1] Appealed from: U.S. Patent and Trademark Office Board of Patent Appeals and Interferences. (Interference No. 102,760).

DISPOSITION: AFFIRMED.

LexisNexis(R) Headnotes

Patent Law > Novelty & Anticipation
Patent Law > Jurisdiction & Review > Standards of Review
[HN1] To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently. Anticipation is a question of fact, and the court upholds decisions of the Board of Patent Appeals and Interferences on factual matters if there is substantial evidence in the record to support the board's findings. Whether a claim limitation is inherent in a prior art reference is a factual issue on which evidence may be introduced. The board's determination of obviousness is a question of law subject to de novo review. However, the board's factual determinations underlying its rulings on anticipation and obviousness are reviewed under the substantial evidence test. Substantial evidence is such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.

Patent Law > Jurisdiction & Review > Standards of Review
[HN2] The Board of Patent Appeals and Interferences' decisions to deny a Motion to Accept Belated Filing and to dismiss a Belated Motion for Judgment are reviewed for abuse of discretion. An abuse of discretion occurs if the decision (1) is clearly unreasonable, arbitrary, or fanciful; (2) is based on an erroneous conclusion of law; (3) rests on clearly erroneous fact finding; or (4) involves a record that contains no evidence on which the board could rationally base its decision.

Patent Law > Jurisdiction & Review > Standards of Review
[HN3] The Board of Patent Appeals and Interferences' legal conclusions regarding priority, conception, and reduction to practice are reviewed de novo.

Patent Law > Novelty & Anticipation
[HN4] Only when a claim is properly understood can a determination be made whether the claim "reads on" an accused device or method, or whether the prior art anticipates and/or renders obvious the claimed invention.

Patent Law > Novelty & Anticipation
[HN5] The court reviews the Board of Patent Appeals and Interferences' legal conclusion, as it does all rulings on claim interpretation, without deference.

Patent Law > U.S. Patent & Trademark Office Prosecution Procedures > Interferences
[HN6] Interference counts are given the broadest reasonable interpretation possible, and resort to the specification is necessary only when there are ambiguities inherent in the claim language or obvious from arguments of counsel.

Patent Law > U.S. Patent & Trademark Office Prosecution Procedures > Interferences
Patent Law > Jurisdiction & Review > Standards of Review
[HN7] What a reference teaches is a question of fact. Therefore, the court reviews the Board of Patent Appeals

and Interferences' characterization of the disclosure in a publication for substantial evidence.

Patent Law > Novelty & Anticipation
[HN8] A reference anticipates a claim if it discloses the claimed invention such that a skilled artisan could take the teachings of the reference in combination with his own knowledge of the particular art and be in possession of the invention.

Patent Law > Novelty & Anticipation
[HN9] Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

Patent Law > U.S. Patent & Trademark Office Prosecution Procedures
[HN10] Copending applications invoke the preponderance of the evidence standard.

Patent Law > Novelty & Anticipation
Patent Law > Jurisdiction & Review > Standards of Review
[HN11] The issue of anticipation -- whether by inherency or otherwise -- is a question of fact, and the court upholds decisions of the Board of Patent Appeals and Interferences on factual matters if there is substantial evidence in the record to support the board's findings.

COUNSEL: Roger L. Browdy, Browdy and Neimark, P.L.L.C, of Washington, DC, argued for appellant.

David S. Abrams, Roylance, Abrams, Berdo & Goodman, L.L.P., of Washington, DC, argued for appellee. With him on the brief was Robert H. Berdo.

JUDGES: Before CLEVENGER, RADER and GAJARSA, Circuit Judges.

OPINIONBY: CLEVENGER

OPINION: [*1055]

CLEVENGER, Circuit Judge.

David M. Rapoport ("Rapoport") appeals from a final decision of the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office ("Board") dated February 29, 2000. The real parties in interest in this interference are: (1) New York University ("NYU"), assignee of Rapoport; (2) the Board of Trustees of the Leland Stanford Junior University ("Stanford"), assignee of William C. Dement ("Dement") and Mark R. Rosekind ("Rosekind"); and (3) the Bristol-Myers Squibb Company ("Bristol-Myers"), assignee of Jeffrey L. Schwimmer ("Schwimmer"). Collectively, Dement, Rosekind, and Schwimmer will be referred to herein as "Dement et al. "

The Board awarded judgment of priority as to the **[**2]** sole count of the interference in favor of Dement et al., and further ordered that Dement et al. are entitled to a patent containing claims 1-13 of U.S. Patent Application No. 07/695,325 ("the '325 application"), filed May 3, 1991, and that Rapoport is not entitled to a patent containing claims 1-12 of U.S. Patent Application No. 07/479,693 ("the '693 application"), filed February 14, 1990. We affirm.

I

The subject matter at issue in this case is a method for the treatment of sleep apnea. Generally, sleep apnea refers to the transient cessation of breathing during sleep. As described by the Board:

> Sleep apneas comprise a spectrum of disorders with varying severity and morbidity and are usually classified as being an obstructive, central, or mixed apnea, depending on the presence or absence of respiratory efforts during the periods in which airflow has ceased. Obstructive and mixed apneas occur with greatest frequency with the most familiar being obstructive sleep apnea syndrome in which sporadic recurring collapse of the patient's upper airway occurs during sleep. If the collapse is complete, there is no air exchange at the nose and mouth and breathing is interrupted. **[**3]** The usual result is a partial arousal and a return to normal breathing.

In most instances, patients suffering from sleep apnea have no knowledge or memory of the apnea episodes, but find themselves constantly suffering from fatigue and daytime drowsiness for no apparent reason. Consequently, due to this chronic lack of proper rest, patients who suffer from sleep apnea often exhibit secondary symptoms of anxiety, depression, fatigue, malaise, irritability, anger, hostility, and other similar problems.

The count in this interference relates to the treatment of sleep apnea by administering a therapeutically effective amount of certain azapirone compounds such as buspirone "to a patient in need of such treatment."

On February 12, 1990, Schwimmer filed U.S. Patent Application No. 07/478,820 ("the '820 application"). Claim 1 of the '820 application as originally filed reads in relevant part:

> 1. A method for treatment of sleep apneas comprising administration of a therapeutically effective regimen of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment . . . .

There is no dispute that although **[**4]** buspirone is an azapirone compound, the azapirone compounds of Schwimmer's Formula I exclude buspirone. On the same day, Dement, Rosekind, and Schwimmer jointly filed U.S. Patent Application No. 07/479,803 **[*1056]** ("the '803 application"). Original claim 1 of the '803 application reads as follows in its entirety:

> 1. A method for treatment of sleep apneas comprising administration of a therapeutically effective regimen of buspirone or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment.

Two days later, on February 14, 1990, Rapoport filed the '693 application. Claim 1 of the '693 application reads as follows in relevant part:

> 1. A method for treatment of sleep apneas comprising administration of a therapeutically effective regimen of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment . . . .

The azapirone compounds of Rapoport's Formula I include buspirone, and claim 6 of Rapoport's '693 application is specifically directed to buspirone.

On February 12, 1991, Schwimmer filed U.S. Patent Application No. 07/657,332 ("the '332 application") **[**5]** as a continuation of the '820 application, and on May 3, 1991, Dement, Rosekind, and Schwimmer jointly filed the '325 application as a continuation-in-part of the '803 and '332 applications. Original claim 1 of the '325 application reads as follows in relevant part:

> 1. A method for treatment of sleep apneas comprising administration of a therapeutically effective amount of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to a patient in need of such treatment . . . .

The azapirone compounds of Formula I in the context of the '325 application include buspirone, and claim 7 of the '325 application is specifically directed to buspirone.

On January 10, 1992, an interference was declared, and Dement et al. were accorded the benefit of the February 12, 1990, filing date of the '820 and '803 parent applications and therefore designated as the senior party. Count 1 of the interference, the only count at issue, reads in pertinent part as follows:

> A method for treatment of sleep apneas comprising administration of a therapeutically effective amount of a Formula I azapirone compound or a pharmaceutically effective acid addition **[**6]** salt thereof to a patient in need of such treatment . . . .

The azapirone compounds of Formula I in the context of the interference count include buspirone. Claims 1-12 of Rapoport's '693 application and claims 1-13 of the Dement et al. '325 application correspond to the count.

On June 10, 1992, Rapoport filed a Motion for Judgment pursuant to 37 C.F.R. § 1.633(a) in which he argued, inter alia, that the subject matter of the count was not patentable to Dement et al., on the grounds that it was anticipated and/or rendered obvious pursuant to *35 U.S.C. § 102*(a) and/or *35 U.S.C. § 103* by a prior art reference authored by Rapoport. This reference, entitled "Buspirone: Anxiolytic Therapy with Respiratory Implications," was published in Family Practice Recertification in September 1989, at pages 32-37 of Vol. 11, No. 9 (Supplement) ("the FPR Publication"). We note that the FPR Publication does not constitute a statutory bar against either Dement et al. or Rapoport, since it was published less than one year before the priority filing date of the '325 and '693 applications. *35 U.S.C. § § 102* **[**7]** (a) and 102(b) (1994). However, because the FPR Publication was authored by Rapoport, it can be cited as prior art against Dement et al., but not against Rapoport. *35 U.S.C. § 102* (1994); *In re Katz, 687* **[*1057]** *F.2d 450, 454, 215 U.S.P.Q. (BNA) 14, 17 (CCPA 1982).* Dement et al. do not contest the fact that the FPR Publication is a prior art reference that may be cited against them in this interference.

On October 29, 1992, pursuant to 37 C.F.R. § 1.602(b), Dement and Rosekind disclosed that they were obligated to assign their rights in the '325 application to Stanford, and Schwimmer disclosed that he was obligated to assign his rights to Bristol-Myers. Approximately eight months later, on June 21, 1993, Dement et al. explicitly stated on the record that Schwimmer was the sole inventor of the use of most of the azapirone compounds covered by the count except

for buspirone in the treatment of sleep apnea. On July 9, 1993, Rapoport filed a Second Motion to Accept Belated Filing Of Preliminary Motion Under 37 C.F.R. § 1.633(a) ("Rapoport's Motion to Accept Belated Filing"), along with a Motion for Judgment **[**8]** Under C.F.R. § 1.633(a) ("Rapoport's Belated Motion for Judgment") arguing that claims in the Dement et al. '325 application are unpatentable under *35 U.S.C. § 102*(g) and/or § 103 over the prior invention of claims 7 and 13 of Dr. Dement, which were invented by a different inventive entity.

On April 12, 1996, the Board rendered a decision which, inter alia, denied Rapoport's June 10, 1992, Motion for Judgment, denied Rapoport's Motion To Accept Belated Filing, and dismissed Rapoport's Belated Motion for Judgment as being untimely. These decisions were adhered to in a decision for reconsideration dated September 6, 1996. The Board rendered its final decision on February 29, 2000.

In its decision dated April 12, 1996, the Board found that: (1) Rapoport had established a conception date of May 13, 1988; (2) Dement was entitled to a 1986 date of conception; and (3) the conception by Dement inures to the benefit of Dement et al. pursuant to *35 U.S.C. § 116.* Based on these findings, the Board awarded priority of the invention of the interference count to Dement et al. Before this court, Rapoport does not contest either the **[**9]** ultimate priority determination in favor of Dement et al. or the underlying findings by the Board.

Instead, on appeal, Rapoport argues that the Board erred in not finding that all of the Dement et al. claims corresponding to the count are either anticipated by the FPR Publication or rendered obvious by the FPR Publication in combination with admissions allegedly made in the Dement et al. '325 application. Rapoport also argues that it was an abuse of discretion for the Board to deny Rapoport's Motion to Accept Belated Filing and to dismiss Rapoport's Belated Motion for Judgment as being untimely. Finally, Rapoport argues that--in the event that this court finds that all of the Dement et al. claims are unpatentable in view of the FPR Publication--the Board erred in awarding judgment on priority in favor of Dement et al. We have jurisdiction to hear this appeal pursuant to *28 U.S.C. § 1295*(a)(4)(A) (1994) and *35 U.S.C. § 141* (1994).

II

[HN1] To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently. *In re Schreiber, 128 F.3d 1473, 1477, 44 U.S.P.Q.2D (BNA) 1429, 1431 (Fed. Cir. 1997).* **[**10]** Anticipation is a question of fact, and we uphold decisions of the Board on factual matters if there is substantial evidence in the record to support the Board's findings. *In re Hyatt, 211 F.3d 1367, 1371-72, 54 U.S.P.Q.2D (BNA) 1664, 1667 (Fed. Cir. 2000).* Whether a claim limitation is inherent in a prior art reference is a factual issue on which evidence may be introduced. *In re Schreiber, 128 F.3d at* **[*1058]** *1477, 44 U.S.P.Q.2D (BNA) at 1431.* The Board's determination of obviousness is a question of law subject to de novo review. However, the Board's factual determinations underlying its rulings on anticipation and obviousness are reviewed under the substantial evidence test. *Dickinson v. Zurko, 527 U.S. 150, 50 U.S.P.Q.2D (BNA) 1930, 144 L. Ed. 2d 143, 119 S. Ct. 1816 (1999); In re Gartside, 203 F.3d 1305, 1316, 53 U.S.P.Q.2D (BNA) 1769, 1775-76 (Fed. Cir. 2000).* Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *In re Gartside, 203 F.3d at 1312, 53 U.S.P.Q.2D (BNA) at 1773* (quoting *Consol. Edison Co. v. NLRB, 305 U.S. 197, 229, 83 L. Ed. 126, 59 S. Ct. 206 (1938)).* **[**11]**

[HN2] The Board's decisions to deny Rapoport's Motion to Accept Belated Filing and to dismiss Rapoport's Belated Motion for Judgment are reviewed for abuse of discretion. *Abrutyn v. Giovanniello, 15 F.3d 1048, 1050-51, 29 U.S.P.Q.2D (BNA) 1615, 1617 (Fed. Cir. 1994).* An abuse of discretion occurs if the decision (1) is clearly unreasonable, arbitrary, or fanciful; (2) is based on an erroneous conclusion of law; (3) rests on clearly erroneous fact finding; or (4) involves a record that contains no evidence on which the Board could rationally base its decision. Id.

As noted above, Rapoport has not requested review of the underlying factual determinations or of the legal bases for the Board's award of priority to Dement et al. Instead, Rapoport merely questions the Board's action of awarding priority to Dement et al. at the same time as holding the Dement et al. claims patentable. This issue involves [HN3] the Board's legal conclusions regarding priority, conception, and reduction to practice, which we review de novo. *Eaton v. Evans, 204 F.3d 1094, 1097, 53 U.S.P.Q.2D (BNA) 1696, 1698 (Fed. Cir. 2000).*

III

We first address Rapoport's argument that the Dement **[**12]** et al. claims corresponding to the count are anticipated by the FPR Publication. Because the first step of a patentability or invalidity analysis based on anticipation and/or obviousness in view of prior art references is no different from that of an infringement analysis, we must start by interpreting any disputed terms in the interference count. Amazon.com, Inc. v. barnesandnoble.com, inc., *239 F.3d 1343, 1351, 57 U.S.P.Q.2D (BNA) 1747, 1751-52 (Fed. Cir. 2001).* [HN4] Only when a claim is properly understood can a determination be made whether the claim "reads on" an

accused device or method, or whether the prior art anticipates and/or renders obvious the claimed invention. Id.

A

Rapoport argues on appeal, as he did before the Board, that it is reasonable to interpret the phrase "method for treatment of sleep apneas" in the interference count broadly to include both (1) treatment of anxiety secondary to sleep apnea and (2) treatment of the underlying sleep disorder itself. In contrast, Dement et al. agree with the Board, which found that in the context of the present interference, treatment of the underlying sleep apnea disorder itself is distinct from treatment of [**13] anxiety and other secondary symptoms related to sleep apnea. Based on this finding, the Board interpreted the term "treatment of sleep apneas" in the interference count as being limited to treatment of the underlying sleep apnea disorder itself. [HN5] We review the Board's legal conclusion, as we do all rulings on claim interpretation, without deference. *Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 U.S.P.Q.2D (BNA) 1169, 1174-75 (Fed. Cir. 1998)* (en banc); *Markman v. Westview Instruments, Inc., 52 F.3d 967, 979, 34 U.S.P.Q.2D (BNA)* [*1059] *1321, 1329 (Fed. Cir. 1995)* (en banc), aff'd, *517 U.S. 370, 38 U.S.P.Q.2D (BNA) 1461, 134 L. Ed. 2d 577, 116 S. Ct. 1384 (1996)*. Upon reviewing the record, we discern no error with the Board's interpretation.

First, we note that the disputed phrase "treatment of sleep apneas" is technically part of the preamble of the interference count, because it appears before the transition word "comprising." However, there is no dispute in this case that the phrase should be treated as a claim limitation. Moreover, without treating the phrase "treatment of sleep apneas" as a claim limitation, the phrase "to a patient in need of such treatment" [**14] would not have a proper antecedent basis.

In support of his proposed broad interpretation for "treatment of sleep apneas," Rapoport relies on the following passage from the written description of the Dement et al. '325 application:

> There are two aspects to the use of azapirones in treating sleep apneas. The first is that the administration of an azapirone effectively reduces the frequency and severity of the apnea episodes during sleep. This is reflected in significantly increased undisturbed sleep and a significant increase in blood oxygen levels. The second aspect involves azapirone alleviation of the symptomatology associated with the occurrence of sleep apneas. The azapirone treatment alleviates the sleep apnea-related symptoms of anxiety, depression, fatigue, malaise, irritability, anger and hostility.

According to Rapoport, this passage supports the notion that "treatment of sleep apneas" in the interference count should include both treatment of the underlying disorder and the "symptomatology associated with the occurrence of sleep apneas." However, to the extent that the above passage suggests that "alleviation of the symptomatology associated with the [**15] occurrence of sleep apneas" constitutes an aspect of the use of azapirones in treating sleep apneas, the intrinsic record in this case leads to the conclusion that "treatment of sleep apneas" refers only to treatment of the underlying sleep apnea disorder.

First, the plain language of the interference count unambiguously refers to "treatment of sleep apneas" narrowly defined, and does not also include by its plain terms "treatment of symptoms associated with sleep apneas." See *Davis v. Loesch, 998 F.2d 963, 968, 27 U.S.P.Q.2D (BNA) 1440, 1444 (Fed. Cir. 1993)* (" [HN6] Interference counts are given the broadest reasonable interpretation possible, and resort to the specification is necessary only when there are ambiguities inherent in the claim language or obvious from arguments of counsel.") (citations omitted); *In re Hyatt, 211 F.3d at 1372, 54 U.S.P.Q.2D (BNA) at 1667* (during examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification). Here, Rapoport relies on the written description of the Dement et al. '325 application in an unsuccessful attempt to broaden the phrase "treatment of sleep apneas" from its ordinary [**16] meaning, which narrowly refers to treatment of the underlying disorder itself.

Contrary to Rapoport's assertions, the written description of the Dement et al. '325 application actually confirms the Board's interpretation, and explicitly defines "sleep apneas":

> In the context of this invention, sleep apneas comprise all the sub-categories such as those caused by upper airway obstruction; those whose origins arise in the central nervous system; and those of a mixed type with contribution from both components.

This passage indicates that the term "treatment of sleep apneas" refers to reducing [*1060] or eliminating sleep apneas caused by upper airway obstructions, sleep apneas whose origins arise in the central nervous system, and sleep apneas of a mixed type.

As further support for the Board's position, the Summary of the Invention in the Dement et al. '325 application states that "for use in the instant method oral administration of a dose of from about 10 to 60 mg of an azapirone at the hour of sleep is usually employed." This description is consistent with treatment of the underlying sleep apnea disorder, which by definition manifests itself during sleep, and inconsistent **[**17]** with treatment of anxiety and other symptoms commonly associated with sleep apnea, which would obviously manifest themselves while a patient is awake.

Next, in a portion of the Detailed Description of the Invention not limited to any particular embodiment, the Dement et al. '325 application states as follows:

> The present invention concerns a method for treating sleep apneas comprising obstructive, central and mixed apneas, in a patient population that ranges from infants to geriatric-aged individuals.

Once again, this passage defines sleep apneas in terms of the underlying respiratory disorder and uses the term "treating sleep apneas" in a manner that is consistent with the Board's interpretation.

Finally, when describing the effectiveness of the sleep apnea treatment method that is disclosed and claimed in the Dement et al. '325 application, the discussion is limited to the treatment's effect on the underlying sleep apnea disorder, and does not mention the treatment's effect on the associated symptomatology:

> The effectiveness of azapirone treatment of patients suffering from sleep apneas can be exemplified by clinical experience with buspirone. Single **[**18]** dose administration of buspirone, given at bedtime to patients suffering from obstructive sleep apnea, resulted in increased sleep efficiency with experimentally derived measurements showing a gain in total sleep time and a marked reduction in episodes of sleep disturbance. One of the most consistent physiological measurements of improvement was a 10 to 20% increase in blood oxygen levels, an indication of improved respiratory efficiency.

In other words, Dement et al. noted that treating patients suffering from obstructive sleep apnea with buspirone at bedtime had a measurably beneficial effect on the underlying sleep apnea disorder (i.e., increased sleep efficiency, gain in total sleep time, significant reduction in episodes of sleep disturbance, and improved respiratory efficiency). However, Dement et al. made no mention in the written description of the '325 application of specific evidence of the treatment's effect on the symptomatology commonly associated with sleep apnea.

We therefore conclude that the Board was correct in interpreting "treatment of sleep apneas" as being limited to treatment of the underlying sleep apnea disorder, i.e., reducing the **[**19]** frequency and severity of the apnea episodes during sleep.

B

Having construed the disputed term in the interference count and affirmed the Board's interpretation, we can properly address the merits of Rapoport's anticipation argument. The Board found that the disclosure of the FPR Publication was limited to treatment of anxiety in patients suffering from sleep apnea with buspirone, and did not address treatment of the underlying sleep apnea disorder. [HN7] What a reference teaches is a question of fact. *In re Beattie, 974 F.2d 1309, 1311, 24 U.S.P.Q.2D (BNA) 1040, 1041-42 (Fed. Cir. 1992).* **[*1061]** Therefore, we review the Board's characterization of the disclosure in the FPR Publication for substantial evidence. *In re Gartside, 203 F.3d at 1316, 53 U.S.P.Q.2D (BNA) at 1775-76.* The record indicates that substantial evidence supports the Board's factual findings regarding the FPR Publication.

There is no disclosure in the FPR Publication of tests in which buspirone is administered to patients suffering from sleep apnea with the intent to cure the underlying condition. As the Board correctly found, the FPR Publication focuses on the treatment of anxiety with buspirone, and indicates **[**20]** that buspirone has potential as a primary treatment for dyspnea (which simply refers to difficulty in breathing in general).

For example, a passage in the FPR Publication mentions the possibility of administering buspirone to patents suffering from sleep apnea, but this is for the purpose of treating anxiety in such patients, not for the purpose of treating the sleep apnea disorder itself:

> Buspirone thus appears to be an anxiolytic agent with a profile of respiratory effects that make it potentially safer to use for patients with impaired respiratory function and for patients with diseases such as obstructive sleep apnea, when use of ventilatory depressants would be clearly dangerous.

Rapoport concedes as much:

> While this passage does not disclose administering buspirone with the intent of treating the sleep apnea per se, such an explicit intent is not necessary in order to anticipate the claims of Dement corresponding to the count.

Rapoport Opening Brief before the Board filed July 5, 1994. In a nutshell, using Rapoport's own words from its Opening Brief before the Board, Rapoport's theory on anticipation is as follows:

> As long as one **[**21]** administers buspirone to a patient with sleep apnea in a therapeutically effective amount, at least claims 1, 2, 6 and 7 of the Dement et al [sic] application underlying the present proceeding are fully anticipated.

In other words, according to Rapoport, neither the reasons for administering buspirone to the patient nor the time of administration are relevant. Instead, according to Rapoport, the only requirement of the count is that the patient suffer from sleep apnea. Given our disagreement with Rapoport's proposed claim interpretation, this argument cannot succeed.

Moreover, the need for tests to confirm safety for treating anxiety in patients with sleep apnea is indicated in the very next sentence of the FPR Publication relating to treating patients suffering from anxiety: "The preliminary results found among healthy subjects need to be confirmed by directly testing patients who need anxiolytic therapy." Thus, even the proposed testing in the FPR Publication is limited to the treatment of patients suffering from anxiety, not from sleep apnea. Moreover, the lack of information concerning administration of buspirone to patients while sleeping is indicated in Table 3 **[**22]** of the FPR Publication, where the entry under "Buspirone" regarding its effect on upper airway tone during sleep is "Undetermined."

The Board also correctly found that the FPR Publication does not show administering buspirone in any specific amounts to patients suffering from sleep apnea. Rather, the FPR Publication discloses administering single oral doses of 10 mg to nine normal volunteers. It also discloses administering buspirone in an amount of 10 mg three times a day to two patients with "severe alveolar hypoventilation" who needed anxiolytic therapy to facilitate use of a nocturnal ventilator. There is no **[*1062]** dispute that none of these patients are reported as suffering from sleep apnea in the FPR Publication.

In contrast, as mentioned earlier, the Dement et al. '325 application discloses that based on clinical experience, administration of a single dose of buspirone at bedtime to patients suffering from obstructive sleep apnea resulted in a marked reduction in episodes of sleep disturbance, and further discloses administration of 20-40 mg of buspirone at the hour of sleep to an average adult.

We note that there is no mention in the FRP Publication of administering buspirone **[**23]** to a patient at bedtime. The significance of this fact, of course, is that sleep apnea, by definition, occurs during sleep. In one of the two tests mentioned in the FPR Publication, a single 10 mg dosage was given at an unspecified time, while in the second test buspirone was administered in doses of 10 mg three times a day, once again without specifying administering the buspirone at bedtime.

Finally, we note that Rapoport argues that the FPR Publication inherently anticipates the count even under the Board's claim interpretation. See *In re Graves, 69 F.3d 1147, 1152, 36 U.S.P.Q.2D (BNA) 1697, 1701 (Fed. Cir. 1995)* (noting that [HN8] a reference anticipates a claim if it discloses the claimed invention such that a skilled artisan could take the teachings of the reference in combination with his own knowledge of the particular art and be in possession of the invention) (citations omitted). According to Rapoport:

> The anxiolytic amount of buspirone taught by the FPR publication still inherently anticipates in view of the fact that the Dement et al. application contains disclosures that anxiolytic amounts of buspirone overlap the preferred therapeutically effective amounts **[**24]** of buspirone disclosed in the Dement et al. application for reducing the frequency and severity of the apnea episodes during sleep.

Specifically, Rapoport bases his argument on the observation that the Dement et al. application specifies administration of buspirone at the hour of sleep in dosages of about 20-40 mg for an average adult. Next, Rapoport notes that the FPR Publication discloses a dosage of 10 mg of buspirone three times a day for treatment of anxiety. The conclusion to be drawn from these observations, according to Rapoport, is as follows:

> The fact that the Dement et al. specification recites a preferred range of 20-40 mg of buspirone administered at the time of sleep does not suggest that the administration of 10 mg of buspirone at

> the time of sleep, particularly when there have been two other dosages of 10 mg each during the course of the day, will have no therapeutic effect. The claims do not require optimal amounts, only therapeutically effective amounts. If 10 mg of buspirone has any effect on the treatment of sleep apnea, even if not optimum, the claim is anticipated.

We conclude that Rapoport's inherency argument is without merit. First, **[**25]** Rapoport neglects to point out that the FPR Publication explicitly states that the patients who received the 10 mg doses of buspirone three times a day were suffering from "severe alveolar hypoventilation who needed anxiolytic therapy to facilitate the use of a nocturnal ventilator," not from sleep apnea. Second, Rapoport's argument is based on at least two speculative assumptions: (1) that a treatment regimen of three doses a day would necessarily include an administration "at the time of sleep;" and (2) that administering two 10 mg doses of buspirone at unspecified times throughout the day in conjunction with a 10 mg dose of buspirone at bedtime would **[*1063]** necessarily result in a "therapeutically effective amount" of buspirone treatment for the purpose of treating the underlying sleep apnea disorder. " [HN9] Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Cont'l Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991)* (emphasis in original) (citations omitted). Rapoport has not attempted to demonstrate that **[**26]** the proposed dosage regimen in the FPR Publication would necessarily result in a therapeutically effective amount. Instead, Rapoport merely argues that the "preferred" range of 20-40 mg described in the Dement et al. application does not rule out the thrice-daily 10 mg doses of buspirone discussed in the FPR Publication in the context of patients who are not even described as suffering from sleep apnea. The burden of proof, of course, is on Rapoport, by a preponderance of the evidence. *Bruning v. Hirose, 161 F.3d 681, 685-86, 48 U.S.P.Q.2D (BNA) 1934, 1937-38 (Fed. Cir. 1998)* ([HN10] copending applications invoke the preponderance of the evidence standard).

Most importantly, however, as we noted at the outset, [HN11] the issue of anticipation--whether by inherency or otherwise--is a question of fact, and we uphold decisions of the Board on factual matters if there is substantial evidence in the record to support the Board's findings. *In re Hyatt, 211 F.3d at 1371-72, 54 U.S.P.Q.2D (BNA) at 1667.* In this case, as detailed above, our review of the record indicates that the Board's findings are amply supported by the evidence. The Board considered the evidence of record and correctly **[**27]** ruled against Rapoport on this issue.

Therefore, for all the reasons stated above, we find that the Board's conclusion that the FPR Publication does not disclose administration of buspirone to patients suffering from sleep apnea to treat sleep apnea is supported by substantial evidence.

IV

Next, we address Rapoport's argument that the Board's action of denying Rapoport's Motion to Accept Belated Filing was an abuse of discretion. As noted earlier, this motion alleged that the Dement et al. claims are either anticipated under *35 U.S.C. § 102*(g) and/or rendered obvious under *35 U.S.C. § 102*(g) and/or § 103 over the prior invention of claims 7 and 13 of Dr. Dement, which were invented by a different inventive entity.

Our review of the record indicates that the Board denied the Motion to Accept Belated Filing on the basis that Rapoport had filed it on July 9, 1993, approximately eight months after Rapoport should have been aware of the facts upon which the motion was based. As the Board correctly noted, Rapoport should have been aware when the interference was declared that the notice of interference accorded Dement et al. the **[**28]** benefit of the abandoned '820 application, wherein Dr. Schwimmer signed an oath stating that he is the sole inventor of the claimed subject matter (i.e., using azapirones other than buspirone to treat sleep apnea). Moreover, the Board correctly indicated that Rapoport learned or should have been aware of the grounds of unpatentability urged in the preliminary motion for judgment on or about October 29, 1992, when Dement et al. filed a notification pursuant to 37 C.F.R. § 1.602(b) stating that Drs. Dement and Rosekind were obligated to assign their entire interest to Stanford and that Dr. Schwimmer was obligated to assign his entire interest to Bristol-Myers.

In view of the above, we conclude that the Board did not abuse its discretion by denying Rappoport's Motion to Accept Belated **[*1064]** Filing or in dismissing the preliminary motion for judgment, because there is evidence of record upon which the Board could base its decision that Rapoport did not show "sufficient cause" why the motion was not filed sooner, as required by 37 C.F.R. § 1.645(b).

V

Finally, we turn to Rapoport's argument that the Board erred in awarding judgment **[**29]** on priority in favor of Dement et al. against Rapoport, notwithstanding the possibility that all of the Dement et al. claims could be ruled unpatentable to Dement et al. As Rapoport

acknowledges, we need not reach this issue, given our conclusion that the Board did not err in finding that the Dement et al. claims were not rendered unpatentable by the FPR Publication.

VI

For the reasons set forth above, the decision of the Board is, in all respects,

AFFIRMED.

CERTIFICATE OF MAILING
I HEREBY CERTIFY
THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231, ON 25 September 1996

Mary E. McCabe
AGENT/ATTORNEY FOR APPLICANT

25 September 1996
DATE

Attorney Docket No. P50317

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Lukas-Laskey, et al.	September 25, 1996
Serial No.:	08/483,635	Group Art Unit No.: 1205
Filed:	June 7, 1995	Examiner: W. Jarvis
For:	METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE	

DECLARATION OF NEIL H. SHUSTERMAN, M.D.

I, NEIL H. SHUSTERMAN, M.D., a citizen of the United States of America, do hereby declare:

1. THAT, I obtained my medical degree in 1978 from Jefferson Medical Center, and that since 1989 I have been employed by SmithKline Beecham Corporation, operating as SmithKline Beecham Pharmaceuticals;

2. THAT, I am presently employed in the capacity of Vice President and Director of the Cardiovascular Therapeutic Unit of Clinical Research, Development and Medical Affairs in Research and Development of SmithKline Beecham Pharmaceuticals, and that I am responsible for the clinical development of carvedilol;

3. THAT, I am a joint inventor in the above-identified patent application and that I am familiar with said application;

4. THAT, the following clinical studies were performed under my direction:

- study 220, a dose response study in moderate (NYHA II-IV) CHF with exercise testing as a primary endpoint
- study 221, a dose titration study in moderate (NYHA II-IV) CHF with exercise testing as a primary endpoint
- study 239, a dose titration study in severe (NYHA III-IV) CHF with quality of life as a primary endpoint
- study 240, a dose titration study in mild (NYHA II-III) CHF with progression of CHF as a primary endpoint

with sixty-four centers in the US participating in the trial program;

5. THAT, the following table summarizes the reduction in mortality for carvedilol-treated CHF patients in the above-noted clinical trials:

	Carvedilol	Placebo	Risk Reduction (95% CI)	p value*
All Cause Mortality	18/624 (2.9%)	29/356 (8.2%)	67% (42-81)	<0.0001
Class II CHF	7/361 (1.9%)	12/202 (5.9%)	68% (20-97)	0.015
Class III-IV CHF	11/263 (4.2%)	17/154 (11.0%)	66% (30-84)	0.004
Ischemic Etiology	10/311 (3.2%)	16/178 (8.9%)	67% (32-85)	0.003
Non-Ischemic Etiology	8/313 (2.5%)	13/178 (7.3%)	67% (20-86)	0.014

* Cochran-Mantel-Haensel Analysis;

6. THAT, this data demonstrates that carvedilol reduces mortality by about 67% in all-cause mortality;

7. THAT, in my opinion, this reduction in all-cause mortality in CHF patients treated with carvedilol is unexpected and significant, since known β-adrenoceptor antagonists had no statistically significant effect on all-cause mortality, as summarized in the table below:

Reference	**Antagonist**	**Observation**
Waagstein, et al., *Lancet*, **342**:1441-1446 (1993) at 1445	metoprolol	no effect on all-cause mortality
CIBIS, *Circulation*, **90**:1765-1773 (1994) at 1771	bisoprolol	failed to demonstrate overall reduction in mortality

8. THAT, in my opinion, the discovery that carvedilol reduced mortality by about 67% in CHF patients satisfies a long-felt need which was recognized, but not solved, by others, as evidenced by the fact that standard agents for treating CHF, such as diuretics, digitalis glycosides, vasodilators (excluding ACE inhibitors), and ionotropic agents, relieve the symptoms of the disease, but are not known to reduce the mortality rate in CHF patients, and that even though ACE inhibitors reduce mortality in CHF patients, this reduction is only on the order of 20%;

9. THAT, in my opinion, one of ordinary skill in the art of medicine reading the data and results presented hereinabove would conclude that carvedilol exhibits a surprisingly and unexpectedly superior property when compared to other agents for treating CHF, and thus that carvedilol provides superior treatment for congestive heart failure, when compared to known agents, since it reduces mortality in CHF patients by about 67%.

10. THAT, I further declare that all the statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Serial No.: 08/483,635
Group Art Unit No.: 1205

Code, and that such willful false statements may jeopardize the validity of the present application or of any patent issuing thereon.

Neil H. Shusterman, M.D.

25 Sep 96

Date

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